



Administering Influenza Vaccine to Egg Allergic Recipients

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Introduction

Renewed interest in the safety of administering egg-containing immunizations to egg allergic children and adults (EA) was prominent during the recent global pandemic of the H1N1 Influenza A virus in 2009-2010. The H1N1 Influenza A vaccine (H1N1), like the seasonal Trivalent Influenza Vaccine (TIV) is grown on embryonated chicken eggs, leading to concerns that residual contamination of ovalbumin could provoke allergic reactivity in EA. The 2010 influenza vaccine has incorporated the H1N1 strains, and thus a single TIV is being offered this season.

Historically, though caution has been recommended in administering influenza vaccine to EA individuals, previous experience suggests that many people with diagnosed or suspected egg allergy can receive influenza vaccination successfully, if precautions are followed. Examples of precautions that have been used include vaccine skin testing, administration via a 2-step graded dose challenging (10%, followed by 90% of the age appropriate dose after a brief observation period), or stepwise desensitization. In some circumstances, egg allergic individuals were advised not to receive the vaccine. Given the urgency to protect children last year from the global influenza pandemic, investigative groups have re-examined the issue of the safety of this vaccine in EA, and the field has advanced significantly since the last influenza season. This paper offers guidance in how to evaluate and treat the patient with egg allergy who desires influenza vaccination, and outlines the latest evidence based approaches to successfully administer the vaccine.

Recent Developments

Within the past year, several studies have helped clarify ongoing questions about the vaccine's safety in EA of any severity, questioning the necessity of skin testing or optimal route of administration, including single dose administration and 2-step graded dose protocols. Two groups separately analyzed the ovalbumin content of vaccine from several vaccine makers, for both H1N1 and TIV. These results showed that TIV lots analyzed contained less than 1.2µg/mL of ovalbumin, and H1N1 less than 0.1 µg/mL.^{1, 2} Previous investigation from the late 1990's demonstrated that TIV lots containing less

than 1.2 µg/mL were well tolerated in EA when administered after skin testing, using a 2-step graded challenge.³ Though there is no study that has demonstrated risk from vaccines containing ovalbumin above this level, many experts urged caution and possibly even withholding the vaccine with higher ovalbumin containing lots.⁴⁻⁶ As well, it appears that many manufacturers have begun to list their ovalbumin content ranges on the package insert, which is of great utility in finding low ovalbumin containing vaccine.⁶

Three studies in the past year have re-examined the approach to vaccinating EA with TIV. One retrospective study of 171 EA without a history of anaphylaxis or severe reactivity attributed to egg showed that the vaccine could be given using a 2-step graded challenge without vaccine skin testing. Seven patients (4%) developed systemic symptoms, and 17% reported localized symptoms.⁷ A large Canadian prospective study, using a unique squalene adjuvanted, low ovalbumin containing H1N1 vaccine (containing less than 0.03 µg/mL ovalbumin), showed that vaccine could be safely administered as a single, age-appropriate dose, without prior vaccine skin testing in 758 EA without a history of severe reaction and 393 non-EA control subjects; and by a 2-step graded challenge (without vaccine testing) in 72 EA with either a history of severe cardiovascular or respiratory symptoms from egg, or uncontrolled asthma. In this study, 17 patients (2%) developed mild symptoms compared to 3.1% in the control group, and there were no reports of anaphylaxis. Based on these favorable results, an additional 3640 patients with self-reported egg allergy were then vaccinated according to the same protocol, with 69 (1.9%) developing symptoms concerning for an allergic reaction, including 2 individuals requiring epinephrine treatment.⁸ Lastly, a single center, controlled prospective study of H1N1 vaccination in 105 EA of all severity, including 25 with a history of anaphylaxis to egg, and 19 non-EA control subjects demonstrated that vaccine skin testing was not predictive of vaccine tolerance, that use of 2-step graded challenge was unnecessary irrespective of past reaction severity to egg, and that booster doses could be safely given from a different lot without vaccine skin testing. Three EA patients (2.4%) and one control subject (5.2%) in this study developed symptoms, none consistent with an allergic reaction. This group further demonstrated that vaccine skin testing was likely to induce an irritant response with increasing vaccine ovalbumin content.⁹ A 4th study with retrospective data from last year's influenza season is close to publication, and echoes the findings of these 3 studies that the vaccine can be successfully administered to EA individuals. (personal communication)

Thus, the work from last season has shown both prospective and retrospective evidence that the vaccine is well tolerated in EA, including limited data in those with a history of a severe allergic reaction to egg, and that vaccine skin testing is not necessary. While there is still some historical debate about the safety of TIV in EA with a history of anaphylaxis or severe reaction to egg, 3 studies, each limited by low numbers of severely egg allergic individuals (n=27, 72, and 25), have demonstrated 2 methods for successfully vaccinating this subgroup. While these results are promising, they must be interpreted cautiously given the sample size. A multi-center trial further evaluating this issue and comparing the methods for administering the vaccine is presently underway in the United States.

Evaluation, of egg allergy

Persons with a history of suspected egg allergy who have an indication for influenza vaccination should first be evaluated by a specialist in food and vaccine allergy. The evaluation should include a detailed history to assess the likelihood that the patient has an IgE mediated sensitivity to egg. If the clinical history indicates a suspicion for egg allergy, then (prick) skin testing to egg, or specific in vitro IgE antibody testing for egg is indicated. With a convincing clinical history and evidence of specific IgE, the diagnosis may be confirmed, but in certain circumstances, oral food challenge to egg may be necessary. Patients with confirmed egg allergy can then receive influenza vaccine using one of the protocols detailed in the following section.

General Recommendations for Vaccinating Egg Allergic Individuals with TIV

The recent research summarized above has shown that the influenza vaccine can be successfully administered to egg allergic individuals via a number of approaches. While there may be no comparative studies that advocate the superiority of one approach over another, the time has passed when the vaccine should be withheld on account of an egg allergy, and providers should be able to choose an approach to vaccinating these individuals with which they are comfortable. In general, though there is no evidence that has conclusively shown that egg ovalbumin is the antigen responsible for adverse reactions to TIV in egg allergic individuals, use of the lowest ovalbumin containing vaccine is recommended.^{5,6} As stated earlier, most manufacturers list their ranges of ovalbumin for their vaccine lots, and studies last year confirmed this range is accurate.^{1,2}

For this influenza season, we no longer recommend the routine practice of skin testing to the TIV. Though skin testing has been used successfully in the past, recent data have indicated that neither prick testing nor intradermal skin testing using the vaccine is predictive of one's ability to tolerate the vaccine, nor was testing necessary to receive a booster dose from a different lot than the original dose.⁹ Furthermore, in two studies published this year, the vaccine was administered safely without the use of skin testing as both a single dose and as a 2-step graded challenge.^{7,8} Therefore, we feel the recent evidence no longer supports TIV skin testing. Skin testing may still be of utility in special cases (e.g., the patient with a documented history of a past allergic reaction specifically to TIV or H1N1 vaccine), as an extra level of caution, though there is no current evidence that has shown skin testing under such settings is necessary or predictive of outcome.

Vaccination Protocols:

We advocate one of two approaches for administering the TIV this season, both of which have been utilized successfully to provide TIV to egg allergic individuals:

- 1) Egg allergic individuals can receive TIV without prior skin testing to the vaccine, with the vaccine being administered via a 2-step graded challenge: first administer 10% of the age appropriate dose, with a 30 minute observation for symptom development. If no symptoms develop, the remainder 90% can be administered, with a 30 minute observation for symptom development. The same TIV product brand should be used for booster vaccinations. Children who need a booster dose can

receive this without prior vaccine skin testing, and as a single dose, regardless if a different lot is used for the booster dose. If reaction is observed at any of the steps, subsequent steps should be withheld, and the patient should be evaluated by an expert in vaccine allergy.

- 2) Egg allergic individuals can receive TIV without prior skin testing to the vaccine, as a single, age-appropriate dose without use of graded challenge. Individuals should be observed for 30 minutes after injection for symptom development. The same TIV product brand should be used for booster vaccinations. Children who need a booster dose can receive this without prior vaccine skin testing, and as a single dose, regardless if a different lot is used for the booster dose.

We recommend either of these approaches as an acceptable way to provide TIV to EA recipients, which should allow for flexibility for patients and providers. Both approaches are supported by recently published evidence that showed the vaccine was successfully given to egg allergic populations. Either approach can be used without mutual exclusion as at present, given neither approach has been proven superior compared to the other. While the evidence is clear that a 2-step approach is well tolerated, there is evidence that a single dose is sufficient for some EA, and speculation that a single dose might have been sufficient in many of these 2-step recipients.

Patients with a History of Anaphylaxis to Egg

There is no clear consensus approach for how to vaccinate individuals with a history of anaphylaxis or severe allergy to egg. The specific American Academy of Pediatrics Red Book recommendations for administration of TIV state “Children with known severe allergic reactions (e.g., hives, angioedema, allergic asthma, or systemic anaphylaxis) to chicken or egg proteins should not receive these vaccines.”¹⁰ However, as we summarized, many children with such histories have received the vaccine previously, without incident.^{3, 8, 9} Two studies from last year’s influenza season showed that past reaction severity is not a risk factor for either H1N1 vaccination or TIV vaccination, and that both vaccine types were well tolerated when administered both as a 2-step graded challenge, or as a single, age-appropriate dose. In one of these studies, skin testing was not predictive of vaccine outcome even in patients with a history of a severe reaction to egg, nor was other allergic co-morbidity (e.g. asthma, atopic dermatitis, or other food allergy). Both studies were limited, unfortunately, by small sample sizes of EA with a history of severe reactivity.

For providers more comfortable administering TIV in a graded step-wise approach, multi-step desensitization protocols for TIV administration have been previously recommended. Present evidence suggests that more than a 2-step administration is unnecessary. In general, a 2 step protocol (10%, 90%) has shown good efficacy and safety for use in administering TIV, and likely is sufficient opposed to a 5 or 6 step protocol. We do caution that 2-step vs. multiple step vaccine administration methods have not been directly compared in formal study. Multiple-step desensitization protocols remain an option for providers that have a particular concern about special select cases,

such as with recipients that have a past history of anaphylaxis to TIV, H1N1, or another egg containing vaccine.

Other Considerations

In previous years, there has been concern that there could be significant differences in ovalbumin content between lots. Thus, it was recommended that patients who needed a booster dose receive this from the same lot to which they were initially tested, or be re-tested if a different lot was to be used. Data from last year's vaccine lots did not reveal large differences in ovalbumin content, and one study found no reactions resulted from deliberate administration of a different lot without testing. Thus, repeat testing for different lots remains an option, but only for those seeking the most conservative approach.

It is strongly recommended that for any provider administering vaccinations, that proper resuscitative equipment is available in the office to manage potential anaphylaxis and that all patients receiving a vaccine are observed for some time interval. Several recent US studies have used 30 minutes as an observation period after a particular dose, though an earlier study used a 60 minute observation period. The recent Canadian study used a 60 minute observation period after the last dose, though this study involved a unique, adjuvanted vaccine, which may explain the expanded observation time. It should be noted in their two described subjects requiring epinephrine treatment, these symptoms developed at or before 30 minutes, though 17 additional patients reported less severe symptoms during the 60 minute time interval. The choice of 30 minutes is modeled after the presently recommended observation interval for receiving subcutaneous immunotherapy

This year, most manufacturers have listed an upper limit of ovalbumin content per 0.5mL dose of TIV. Table 1 details these stated ovalbumin level as listed in the package inserts for the various approved vaccines for the 2010-2011. We provide this table as a reference to help clarify the approximate ovalbumin content per dose, to help better guide the selection of product to use in the egg allergic patient. In considering both individual vaccine product selection and the two approaches for providing the vaccination described above, the Canadian study did provide evidence that lower risk EA patients were able to successfully receive a low ovalbumin containing product as a single dose. Furthermore, in that same study, higher risk patients (based on past egg allergy severity) were able to safely receive the same low ovalbumin containing vaccine given as a 2-step graded challenge. Such "risk stratification" is a very reasonable approach. Comparatively, however, James et. al and Greenhawt et al. were able to safely administer vaccine with higher ovalbumin content to both higher and lower risk patients using either the single step or the 2-step approach, highlighting that no one particular approach is superior at present.

Conclusion

There has been tremendous growth over the past year in demonstrating that TIV (and H1N1) are safe for egg allergic individuals to receive. While a few concepts bear further study, such as the safety of these vaccines in individuals with severe allergy to egg, it

appears that most egg allergic patients can safely receive influenza vaccination if desired. While no particular approach to administering the vaccine has been shown to be the safest and most effective, several methods for providing this service exist. Providers should no longer withhold the vaccine on account of a patient's egg allergy, and should feel comfortable selecting one of two strategies we outline for administering the influenza vaccine.

Table 1: Approved 2010-2011 Influenza Vaccines Ovalbumin Content Levels

Product	Manufacturer	Age Range	Ovalbumin Content Listed in Package Insert*
Afluria	CSL Biotherapies (Merck)	9 years and older	$\leq 1 \mu\text{g}$
Agriflu	Novartis	18 years and older	$< 0.4 \mu\text{g}$
Fluarix	GlaxoSmithKline	3 years and older	$\leq 0.05 \mu\text{g}$
FluLaval	ID Biomedical Corp. of Quebec (GSK)	18 years and older	$\leq 1 \mu\text{g}$
FluMist (nasal)	MedImmune	2 years to 49 years	Level not listed
Fluvirin	Novartis	4 years and older	$\leq 1 \mu\text{g}$
Fluzone, Fluzone HD	Sanofi Pasteur	6 mo and older	Level not listed

*All levels per 0.5mL dose

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